

# Current recommendations for *Helicobacter pylori* therapies in a world of evolving resistance

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Occurrence of resistance, especially to clarithromycin, renders the standard triple therapy used to cure *Helicobacter pylori* infection ineffective. This review presents the bacteriological and pharmacological basis for *H. pylori* therapy and the current recommendations. The third-line treatment must be based on clarithromycin susceptibility testing. If the bacteria are still susceptible, failure may come from problems of compliance, hyperacidity or high bacterial load which can be overcome. If the bacteria are resistant, different regimens must be considered, including bismuth and non-bismuth-based quadruple therapies (sequential or concomitant), as well as triple therapies where amoxicillin is administered several times a day to obtain an optimal concentration at the gastric mucosal level. The treatments are becoming more and more complex and ecologically unsatisfactory, waiting for new agents or vaccines.

## Introduction

The discovery of *Helicobacter pylori* and of the role of *H. pylori* infection in the main diseases of the stomach led to the impression that we could rapidly get rid of these diseases by using antimicrobials and eventually a vaccine. In 1993, an effective therapy was finally proposed based on the association of two antibiotics: clarithromycin and amoxicillin or metronidazole, and an antisecretory drug essentially a proton pump inhibitor (PPI).<sup>1,2</sup> This regime has been confirmed efficacious in large multicenter trials<sup>3,4</sup> and recommended by the various consensus conferences held around the world.<sup>5–7</sup>

However, it now appears that the aim was not achieved as simply as that because *H. pylori*, like other bacteria, can become resistant to antibiotics and we are now faced with numerous failures which make the use of this clarithromycin-based standard triple therapy unacceptable in many parts of the world.

In this review, the rationale for the current strategies of *H. pylori* treatment as well as the latest guidelines will be presented.

## Basis for *H. pylori* Eradication Treatment

The aim of the treatment is to obtain a mucosal concentration of the antibiotic against *H. pylori* above the minimal bactericidal concentration (MBC) at the site of the infection, i.e., the gastric mucus, and during a sufficient time lapse to eradicate all of the bacteria present. For practical reasons, the minimal inhibitory concentration (MIC) is used as a surrogate of MBC.

Bacteriological data first indicated the antibiotics with the best potential: macrolides (especially clarithromycin),  $\beta$ -lactams (essentially amoxicillin), tetracycline, metronidazole, rifampins (essentially rifabutin) and later fluoroquinolones (especially levofloxacin). The MICs of these drugs against *H. pylori* are low (Table 1) (EUCAST: [http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST\\_files/Consultation/EUCAST\\_clinical\\_breakpoints\\_for\\_Helicobacter\\_pylori.pdf](http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/EUCAST_clinical_breakpoints_for_Helicobacter_pylori.pdf)) and a mucosal concentration above the MIC can be expected by taking therapeutic doses. Dosages in the gastric mucosa have been performed for some of them and support the postulate. Furthermore, clinical trials have confirmed the experimental data.

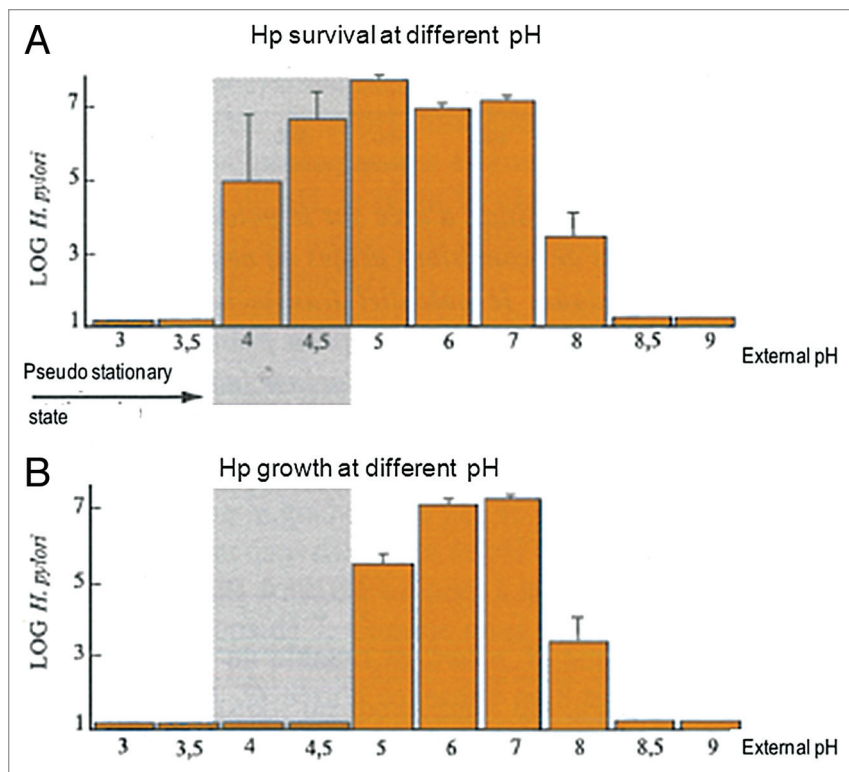
However, it was also shown that the drugs need to be absorbed and released in the gastric mucosa over long periods. The aminoglycosides, which are not absorbed despite their in vitro activity, are not usable and for the same reason bismuth salts which have an antimicrobial activity cannot be used as the sole drug.

It is important to note that a few drugs do not lead to good clinical results despite their belonging to the antibiotic groups considered active. Such is the case for doxycycline among the tetracyclines<sup>8</sup> and ciprofloxacin among the fluoroquinolones.

Another point to consider is the acidity of the stomach. There is a pH gradient from 7.2 to 2 in the gastric mucus where *H. pylori* lives. *H. pylori*, while not a true acidophile, may still proliferate at pH 5 and survives at pH 4 (Fig. 1).<sup>9,10</sup> Most of the antibiotics are not active at low pH, and are only active on dividing bacteria, so it is necessary to add an antisecretory drug to increase the pH of the stomach, and a double-dose of PPI has been the most valuable addition.

The amoxicillin concentration detectable in gastric juice is in the range of this drug's MIC against *H. pylori*. The concomitant PPI treatment, by decreasing the gastric juice volume, will increase its efficacy. In contrast, clarithromycin is able to concentrate in gastric juice compared with blood but a PPI does not increase the gastric transfer fraction. Metronidazole is the drug

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**Figure 1.** Survival (A) and growth (B) of *H. pylori* according to pH.<sup>10</sup>

**Table 1.** EUCAST proposed breakpoints for *Helicobacter pylori*

Agent	Susceptible (mg/L)	Resistance (mg/L)
Amoxicillin	≤ 0.12	> 0.12
Clarithromycin	≤ 0.25	> 0.5
Levofloxacin	≤ 1	> 1
Tetracycline	≤ 1	> 1
Rifampin	≤ 1	> 1
Metronidazole	≤ 8	> 8

which concentrates the most in gastric juice. It has been explained by the pH partition hypothesis, i.e., weak bases are trapped in the acidic compartment of the stomach. Metronidazole is indeed predominantly unionized at neutral pH (in blood) but ionizes as the pH decreases (in the gastric mucosa) and then does not diffuse anymore through membranes. Accordingly, the gastric transfer fraction decreases when taking a PPI but is still significant, because the pH remains moderately acidic.<sup>11</sup>

A sufficient concentration of the antibiotic must be maintained in the mucus over a long period of time. In this respect, the antibiotics which have an intracellular diffusion like clarithromycin have an advantage because the antibiotic can then be gradually released from the epithelial cells in the mucus while for those without intracellular diffusion, e.g., amoxicillin, a permanently high blood concentration is needed to obtain a sufficient concentration of the drug in the mucosa probably via a paracellular pathway (Fig. 2).<sup>12,13</sup>

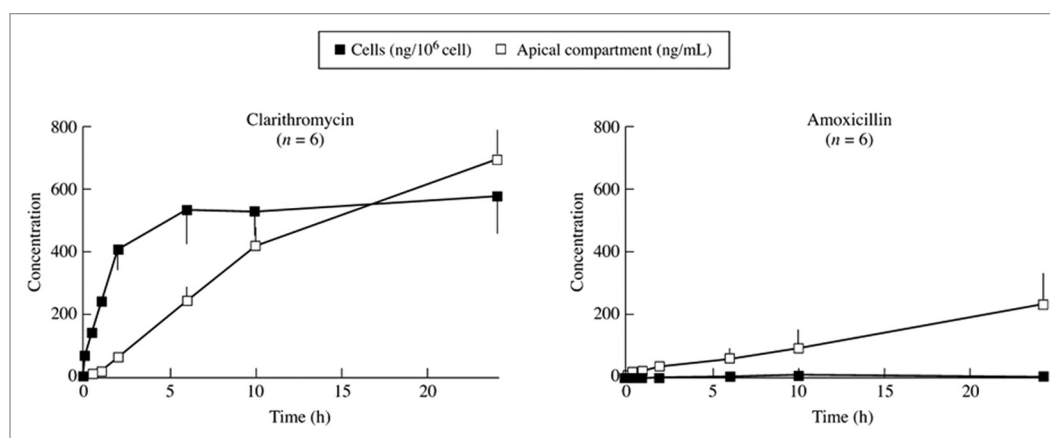
All of the data obtained have established that clarithromycin, a macrolide derived from erythromycin, is indeed the basis for *H. pylori* treatment because of its low MIC, good mucosal diffusion, and limited effect of the acidity. However, it was also shown that a second antibiotic should be added to obtain high and permanent eradication rates, either amoxicillin which also has excellent MICs but limited intracellular diffusion, or metronidazole, a small molecule which concentrates in the mucus as seen before. This standard triple therapy was satisfactory for many years but is now faced with the problem of *H. pylori* resistance to clarithromycin.

*H. pylori*, like all bacteria, is able to become resistant to antibiotics. Fortunately, the genetic basis is not the spread of genetic elements (plasmids, transposons) which can lead to a horizontal transfer as an epidemic in a population of bacteria, but essentially a selection of bacteria with point mutations which occur mostly by chance during the replication process.<sup>14</sup>

Clarithromycin acts by inhibition of protein synthesis at the ribosomal level. A mutation at certain positions on the 23S rRNA gene modifies the structure of the ribosomes inhibiting clarithromycin binding at the level of the peptidyl transferase loop, and leads to higher MICs than what can be achieved by a therapeutic dose.<sup>15,16</sup> There is cross resistance for all of the other macrolides. Clinical trials have shown that the rate of success of the standard triple therapy in many regions is now in the range of 70%, and is much lower when the *H. pylori* strain is resistant vs. susceptible (20% vs. 90%, respectively).<sup>17</sup>

The other antibiotic for which resistance is important to consider is levofloxacin. This antibiotic has been proposed to replace clarithromycin in rescue treatments and is indeed efficacious. It inhibits the A subunit of the gyrase encoded by the *gyrA* gene of *H. pylori*, an enzyme which unravels DNA to allow DNA replication. The occurrence of a point mutation in a special region of the *gyrA* gene, the so-called quinolone resistance determining region (QRDR), leads to a modification of the target and an increase in MIC, which cannot be overcome by the concentration of the antibiotic in the mucosa.<sup>18,19</sup> There is also cross-resistance for all fluoroquinolones. Clinical trials have shown the efficacy of a PPI-amoxicillin-levofloxacin therapy.<sup>20</sup> Later it was shown that the success of this regimen decreases radically in the case of levofloxacin resistant compared with levofloxacin susceptible *H. pylori*.<sup>21</sup>

For several drugs eventually used to treat *H. pylori* infection, resistance is rare. Resistance to rifampins (point mutations on the *rpoB* gene)<sup>22</sup> may be found in patients previously treated with rifampicin especially for tuberculosis.<sup>23</sup> Resistance to tetracycline requires the change in a nucleotidic triplet occurring on the 16S rRNA gene which inhibits tetracycline binding to the h1 loop,<sup>24</sup> a very rare event indeed, seldomly reported except in Korea and



**Figure 2.** Long-term basal-to-apical (serosal-to-mucosal) transport of clarithromycin and amoxicillin across HT29-19A cell monolayers in cell culture inserts (mean  $\pm$  s.d.).<sup>12</sup>

Brazil.<sup>25,26</sup> However, in both countries there are also reports indicating a low prevalence of resistance to this antibiotic.<sup>27,28</sup> Only a few amoxicillin resistant strains have been found due to mutations in the *pbp1* gene<sup>29</sup> and it is possible that those strains labeled resistant in some reports but with no further investigation are not truly resistant.

A special mention must be given for metronidazole. Metronidazole is a prodrug, which must be reduced to hydroxylamine inside the bacterial cell by different enzymes to cause DNA breaks.<sup>30</sup> This reduction is very much dependent on the redox potential inside the cell which itself depends on the redox potential in the environment, a characteristic which is neither controlled in vivo nor in vitro during testing. Therefore, there is a problem of reproducibility in the MIC measures performed for metronidazole.<sup>31</sup> This fact, in addition to the poor correlation observed between the in vitro and the in vivo data, led to consider metronidazole resistance as irrelevant and its testing is not recommended at an individual level in routine practice.<sup>32</sup> However, we must recognize that at the population level metronidazole resistance does have some impact which is much less than that of clarithromycin and levofloxacin, and is also dependent on the other drugs used as well as the length of treatment. Tinidazole has the same bacteriological activity as metronidazole on *H. pylori*.<sup>33</sup> However, it has a significantly longer half-life and lower total clearance.<sup>34</sup>

In addition to the question of *H. pylori* resistance, it appears to be important to evaluate the consequence of the intervention, i.e., *H. pylori* eradication, on the general microbiota of the patient but there are no data on this topic yet. Studies performed in Sweden have shown the impact of the standard clarithromycin-based triple therapy on the resistance of some bacteria present in the flora from saliva and intestine. Samples showed an increase in amoxicillin MICs for *Streptococcus* sp., *Staphylococcus* sp. and *Enterococcus* sp. and an increase in clarithromycin MICs also for *Enterobacteriaceae* and *Bacteroides* sp., while a suppression of other anaerobic bacteria occurred. Persistence of high level clarithromycin resistant enterococci were found for 3 y in 3 out of 5 patients in a long-term follow-up.<sup>35,36</sup>

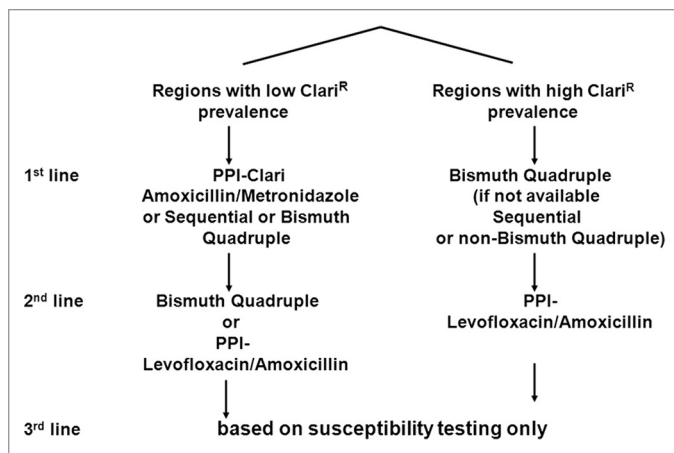
## Current Recommendations for Treatment

The prevalence of *H. pylori* resistance to clarithromycin which is the main risk factor for the success of the standard *H. pylori* eradication therapy prescribed empirically is highly variable between countries or regions throughout the world. The prevalence depends on the selection pressure of the corresponding group of antibiotics in a given area. In Europe a significant correlation has been shown between the consumption of long acting macrolides in the community, expressed as a defined daily dose per 1000 inhabitants per day, and the proportion of *H. pylori*-resistant strains.<sup>37</sup>

Antibiotic resistance mediated by chromosome mutations is vertically transmitted, to the descendants. Apparently, for macrolides, there is limited biological cost to the bacterium, or compensatory mutations can occur<sup>38</sup> which explains why they can be maintained even when the selective agent is absent. European surveys performed at 10 y intervals showed that *H. pylori* resistance increased by approximately 1% per year, from 9.9% in 1998<sup>39</sup> to 17.5% in 2008–2009.<sup>37</sup> A similar increase in clarithromycin resistance has also been documented in the Far East (Japan, Korea)<sup>25,40</sup> while there are few data concerning the US.

Based on these results, the recommendation is to follow a different empiric treatment strategy according to the level of primary clarithromycin resistance observed, the threshold ranging from 15–20% (Fig. 3).<sup>32</sup> For regions with low clarithromycin resistance, the recommendation is to continue the use of standard triple therapy as a first-line treatment and, in the case of failure, to choose either a bismuth-based quadruple therapy or a PPI-levofloxacin-amoxicillin therapy as a second-line treatment.

To the contrary, for regions with a high clarithromycin resistance, the first option is a bismuth-based quadruple therapy. If bismuth is not available, a non-bismuth quadruple therapy could be used, preferably as a sequential therapy. This sequential therapy is comprised of 5 d of PPI-amoxicillin followed by 5 d of PPI-clarithromycin-metronidazole.<sup>41</sup> Resistance to clarithromycin only slightly affects the outcome of the treatment, the rationale being that the PPI-amoxicillin course already eliminates most of



**Figure 3.** Therapies recommended for *Helicobacter pylori* eradication. Maastricht-4 Consensus Report.<sup>32</sup>

the bacteria, decreasing the chance of encountering a mutation since the rate of mutation for clarithromycin is in the range of  $(10^{-9})$ .<sup>42</sup> It has also been proposed to give the 4 drugs concomitantly. However, in the case of clarithromycin resistance, only the 2 other antibiotics are effective. In the case of failure of this first-line therapy, a PPI-levofloxacin-amoxicillin combination can be used. A limit of the empiric strategy is the use of levofloxacin for which resistance is emerging in many places, again due to the widespread use of this family of drugs in the community.<sup>37</sup>

These recommendations are an extension of the previous guidelines published in Europe<sup>43</sup> and USA in 2007.<sup>44</sup>

### What to Do When Empiric Treatment Fails Twice?

According to the current recommendations,<sup>32</sup> when an empiric treatment fails twice, it is necessary to prescribe a tailored treatment, i.e., the antibiotic susceptibility of *H. pylori* should be tested in order to prescribe the most adapted regimen, and tools are available for this purpose.<sup>45-47</sup>

All bacteriology laboratories are indeed able to culture *H. pylori*. The pre-analytic phase is crucial, i.e., the obtention of gastric biopsies which must be taken from both the antrum and the fundus before taking biopsies for pathology, followed by their introduction into a transport medium maintained at 4°C, because temperature, desiccation and contact with air are harmful for the bacteria. Recommendations for culture and susceptibility testing either by disk diffusion or E-test have been published.<sup>14</sup> The minimal testing is for clarithromycin and levofloxacin, and possibly other antibiotics depending on the area concerned.

This traditional approach is demanding in the lab and a delay of several days is necessary to obtain the results. Molecular methods using mainly PCR have been developed to detect the point mutations responsible for clarithromycin resistance. Several PCR formats exist. An interesting one is the real-time PCR using the fluorescence resonance energy transfer principle (FRET-RT-PCR). This FRET-RT-PCR allows first a detection of *H. pylori* if an amplification occurs and second the possibility to perform a melting curve analysis of the amplicons once obtained. The

presence of a mutation is responsible for a DNA mismatch and consequently a lower melting temperature, so it is easy to detect in comparison to the wild type.<sup>48</sup> There are commercial kits available for this purpose which can also be used on faeces. A non-PCR method, a fluorescence in situ hybridization (FISH) technique, can also be performed on histological preparations; it detects *H. pylori* with one probe and clarithromycin resistance with another probe.<sup>49</sup>

Given the high number of mutations which can lead to levofloxacin resistance, another approach has been developed: a multiplex PCR followed by DNA hybridization on a strip.<sup>50</sup> This commercially available method can detect mutations responsible for both levofloxacin and clarithromycin resistance.

### What if the strain is still susceptible to clarithromycin?

Clarithromycin resistance occurs in approximately two thirds of the cases of failure with standard triple therapy so susceptibility is not unusual, still present in one third of the cases. On the other hand, in the case of a clarithromycin susceptible strain before treatment, a 100% eradication rate is seldomly obtained due to other potential causes which, while not frequent, can be responsible for failure of the standard triple therapy. However, triple therapy can still be used after correcting the following problems.

The first is compliance and for this we have to rely on the patients' claims which are difficult to verify. A study using special containers (Medication event monitoring System) showed that there were more than 10% of poor compliers (i.e., taking less than 85% of the total amount of drugs) leading to much lower eradication rates.<sup>51</sup> *H. pylori* treatments are relatively complex compared with others, so it is important to convince the patient to follow the prescription and to inform him/her of potential adverse events which are common and should not lead to stopping the treatment. There is room for improvement in this field, especially with general practitioners who are not often faced with this type of patient and who need to be taught by the specialists.

Another possible reason is that we are dealing with an acid hypersecretor patient for whom the quantity of PPI prescribed is not sufficient to obtain an adequate pH for the antibiotics to be active. Independently of gastrinoma, such patients have been described in the past.<sup>52</sup>

There is also the possibility of patients who are rapid PPI metabolizers. PPI are metabolized in the liver by the cytochrome P450 isoenzyme CYP2C19 for which polymorphisms do exist and patients can be separated into rapid, intermediate and low metabolizers. Rapid metabolizers may have a pH one point lower than the low metabolizers, when taking the same dose of PPI.<sup>53</sup> The proportion of *H. pylori* eradication using standard triple therapy was only 64.7% for the rapid metabolizers vs. 79.4% and 100% for the intermediate and low metabolizers, respectively, indicating the need for a higher dose of PPI in a recent study.<sup>54</sup> The frequency of rapid metabolizers in the Western populations remains however to be determined.

A higher bacterial load, determined by the DOB value of the semi-quantitative test, i.e., the urea breath test, has also been shown to be a cause of more frequent failures.<sup>55</sup>



The CagA negative status is also a potential risk factor for failure, possibly because these strains may not replicate as quickly as the CagA positive.<sup>56</sup> Furthermore, this may explain the constant finding of superior eradication rates in patients with peptic ulcer disease vs. those with non-ulcer dyspepsia.<sup>57</sup>

Under such circumstances, only increasing dosages and the duration of treatment can be done.

#### What if the strain is resistant to clarithromycin?

This situation is indeed the most frequent and there are several possibilities to be reviewed for each given patient, none of which is a panacea.

##### *Bismuth-based quadruple therapy*

The patient has most likely already received this regime but it must be noted that there is now a commercially available 3-in-1 capsule (Pylera®), prescribed with a PPI for 10 d. This galenic form favors compliance and the 10 d treatment duration can be superior to the 7 d which the patient may have received.<sup>58</sup> This regimen has shown excellent results independently of the metronidazole resistant status of the strain (Fig. 4).

##### *Sequential or concomitant non-bismuth quadruple therapies*

Clarithromycin resistance has a limited impact on the sequential treatment so, theoretically, it could be used.<sup>41,59</sup> However, recent trials from Asia were not all as promising as the previous ones.

The so-called concomitant therapy has the advantage to favor compliance. It was successful in several trials and especially on clarithromycin resistant strains in a Spanish trial.<sup>60</sup> A review of this therapy involving 2070 patients from 19 studies obtained a mean eradication rate of 88%.<sup>61</sup>

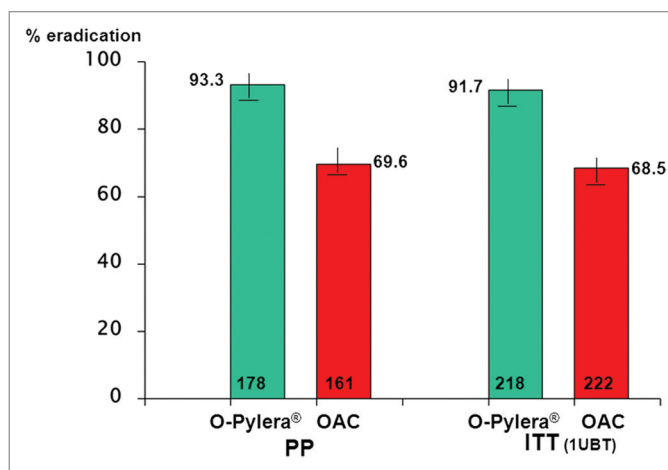
There are also some attempts to combine the 2 approaches, sequential and concomitant, by prescribing a 14-d sequential regimen but continuing amoxicillin during the entire period, the so-called hybrid therapy.<sup>62</sup>

The sequential and concomitant regimens were compared with the standard triple therapy in a large trial performed in six Latin American countries. Surprisingly, the best results were obtained with the standard triple therapy (82.2% eradication intention to treat) surpassing concomitant therapy by 8.6% and sequential therapy by 5.6%. These treatments were all given empirically, so results of clarithromycin susceptibility are not available.<sup>63</sup>

##### *PPI-amoxicillin-levofloxacin for 10 d*

If the patient already received this treatment, levofloxacin resistance is almost always present after treatment failure. Otherwise it is an option, and even better following testing. This regimen has mainly been used as a second-line treatment. A large study performed in Spain led to a 73.8% eradication rate,<sup>64</sup> as well as 78.1% in Taiwan.<sup>65</sup> A metaanalysis even showed this regimen to be superior to bismuth-based quadruple therapies.<sup>66</sup>

Beside levofloxacin, moxifloxacin has also been used successfully,<sup>67</sup> but it is now recommended to limit the use of this drug in several countries due to various adverse events. There are promising data from Japan especially with sitafloxacin, a fluoroquinolone with higher efficacy especially in case of resistance associated mutations<sup>68</sup> and active at acidic pH. In a large multicenter trial in Japan, in patients receiving a third-line therapy in



**Figure 4.** *H. pylori* eradication with Pylera®-omeprazole (10d) vs. standard clarithromycin-based triple therapy (7d) European Multicentric Study.<sup>58</sup>

PPI-amoxicillin-sitafloxacin led to a 70% eradication rate ITT.<sup>69</sup> Another fluoroquinolone, gemifloxacin, appears to have the same property to overcome quinolone resistance.<sup>70</sup>

##### *PPI-amoxicillin-metronidazole for 14 d*

This old regimen can lead to good eradication rates. It is frequently used in Japan as a second-line treatment. Data from 1373 patients from 15 sites in the Tokyo Metropolitan area during 5 y were compared. There was no significant trend for decrease efficacy with an overall eradication rate of 92%.<sup>71</sup> It can also be improved by increasing the number of times amoxicillin is taken because, as mentioned before, it is important to maintain a high blood concentration of amoxicillin to maintain a gastric mucus concentration higher than the MIC.

Furuta et al. compared a PPI amoxicillin-metronidazole therapy with amoxicillin administered bid (750 mg), tid (500 mg) and qid (500 mg). They obtained an eradication rate of 82.1%, 96%, and 100%, respectively.<sup>72</sup>

##### *PPI-amoxicillin-rifabutin*

Rifabutin has not the best safety profile. Rifabutin is toxic to the blood cell lineage leading to neutropenia and thrombocytopenia and furthermore, it is better to reserve it for mycobacterial infections. This regimen should be considered only if everything else has failed.

A PPI-amoxicillin-rifabutin therapy, used as a rescue therapy after 3 failures in 2 studies, led to a 50% eradication rate only.<sup>73,74</sup>

##### *PPI-amoxicillin*

There is also a comeback of this dual therapy from the early days but with some adaptations, because as mentioned above, it is important to maintain a high blood concentration during the nycthemeral cycle. Furuta et al. succeeded by administering the drug 4 times a day instead of twice a day.<sup>75</sup>

Other antibiotics are also used but not available in many countries such as furazolidone, which can be used in bismuth-based quadruple therapy instead of metronidazole, but has side effects, especially in case of high dosage, rifaximin, a non-absorbed antibiotic of the rifampin group, nitazoxanide, a drug related to

metronidazole. Currently there is a trend to mix different drugs in order to get high eradication rates.

The interest in adding an adjuvant therapy, such as probiotics is also questioned. Certain probiotics, such as *Loctobacillus reuteri*, have a potent anti-*H. pylori* activity in vitro but none were able to eradicate *H. pylori* in animal models. It is accepted that the benefit obtained with probiotics is essentially by their capacity to prevent side effects, especially diarrhea. The metaanalyses performed have shown an increase in eradication of about 5–10%.<sup>76,77</sup>

All these treatments are not usable in all patients. The problem of  $\beta$ lactam allergy in some patients restricts the possibilities. In this respect, replacing amoxicillin by tetracycline may be worth considering. A PPI-tetracycline-metronidazole has shown to be effective.<sup>78</sup> In children fluoroquinolones and tetracyclines cannot be used and therefore limit considerably the possibilities. As first line treatment, either PPI-amoxicillin-imidazole or PPI-amoxicillin-clarithromycin or bismuth salts-amoxicillin-imidazole or sequential therapy is recommended. Susceptibility testing is also recommended for clarithromycin before using this

antibiotic in areas of known high resistance. After failure, a tailored treatment is recommended as well as increasing dose and/or duration of therapy.<sup>79</sup> In obese patients the eradication rate appears to be inferior to the normal population<sup>80</sup> possibly because of an increased distribution volume.

## Conclusion

Our possibilities are currently limited by the lack of new drugs. All attempts tend to get the best results from old antibiotics by combining them in different ways, and so treatment success is obtained at an ecological cost for the human microbiome. There is however, room for improvement in general practice by following current guidelines including follow-up control by performing a urea breath test after 4 to 6 weeks. It is also important to keep in mind that in some cases immediate eradication is not mandatory, and can be delayed, hoping for better drugs in the future.

## Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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